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RESEARCH ARTICLE

Left dorsolateral prefrontal cortex atrophy is associated with frontal lobe function in Alzheimer's disease and contributes to caregiver burden

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Objective: Caregivers of patients with dementia experience physical and mental deterioration. We have previously reported a correlation between caregiver burden and the Frontal Assessment Battery (FAB) total scores of patients with Alzheimer's disease (AD), especially regarding the dependency factor from the Zarit Burden Interview. The present study aimed to identify an objective biomarker for predicting caregiver burden.

Methods: The participants were 26 pairs of caregivers and patients with AD and mild-to-moderate dementia. Correlations between regional gray matter volumes in the patients with AD and the FAB total scores were explored by using whole-brain voxel-based morphometric analysis. Path analysis was used to estimate the relationships between regional gray matter volumes, FAB total scores, and caregiver burden based on the Zarit Burden Interview.

Results: The voxel-based morphometric revealed a significant positive correlation between the FAB total scores and the volume of the left dorsolateral prefrontal cortex. This positive correlation persisted after controlling for the effect of general cognitive dysfunction, which was assessed by using the Mini-Mental State Examination. Path analysis revealed that decreases in FAB scores, caused by reduced frontal lobe volumes, negatively affected caregiver burden.

Conclusions: The present study revealed that frontal lobe function, based on FAB scores, was affected by the volume of the left dorsolateral prefrontal cortex. Decreased scores were associated with greater caregiver burden, especially for the dependency factor. These findings may facilitate the development of an objective biomarker for predicting caregiver burden.

KEYWORDS

Alzheimer's disease, caregiver burden, dementia, dorsolateral prefrontal cortex, frontal lobe function, magnetic resonance imaging

1 | INTRODUCTION

Some studies have revealed that most patients with Alzheimer's disease (AD) receive care from their relatives.[1] However, caregivers for patients with AD experience physical and mental deterioration, which can lead to depression,[2-5] decreased quality of life,[6,7] and coronary heart disease.[8] Furthermore, behavioral problems that are caused by frontal dysfunction can predict caregiver burden.[9] In our previous study, we observed that the Frontal Assessment Battery (FAB) scores of patients with AD were correlated with caregiver burden, especially for the dependency factor.[10]

The FAB was developed as bedside tool for assessing frontal lobe function.[11] This tool explores various aspects of frontal lobe function, such as conceptualization, abstract reasoning, mental flexibility, motor programming, executive control of action, resistance to interference, self-regulation, inhibitory control, and environmental autonomy. However, there is controversy regarding whether FAB scores actually reflect frontal lobe function. One study failed to

identify associations between FAB scores and frontal lobe perfusion,[12] while other studies revealed associations with general cognitive decline, which was assessed by using the Mini-Mental State Examination (MMSE).[13,14] Therefore, based on our previous finding that FAB scores were correlated with caregiver burden, the present study aimed to identify a biomarker that could be evaluated by using magnetic resonance imaging (MRI). Our hypothesis was that FAB total scores would be correlated with frontal lobe volumes, independent of general cognitive dysfunction, and our path analysis revealed that lower FAB scores, caused by reduced frontal lobe volumes, negatively affected caregiver burden.

Key points

- Frontal Assessment Battery total scores were positively correlated with the volume of the left dorsolateral prefrontal cortex.
- This correlation persisted after controlling for the effect of general cognitive dysfunction based on the Mini-Mental State Examination.
- Path analysis revealed that decreased Frontal Assessment Battery scores, caused by reduced frontal lobe volumes, negatively affected caregiver burden.
- These findings may facilitate the development of a biomarker for predicting caregiver burden.

2 | METHODS

2.1 | Subjects

The present study examined MRI data from 26 patients with AD, as well as interview data from their caregivers, who had participated in our previous study at the hospital of Nara Medical University.[10] All patients had mild-to-moderate dementia and had been recruited from geriatric psychiatric outpatient clinics at the hospital of Nara Medical University. All patients were diagnosed with probable AD by using the criteria of the National Institute on Aging and the Alzheimer's Association[15] and had undergone MRI at that hospital. Patients were excluded if they had any non-AD neurodegenerative disease (eg, dementia with Lewy bodies, Parkinson's disease, or Huntington's disease, or fronto-temporal dementia), or if they had significant hearing or visual impairments that could have complicated the interviews. Each caregiver fulfilled the following inclusion criteria: (1) a relative of the patient, (2) familiar with the patient's daily activities, and (3) agreed to be interviewed. This study's protocol was approved by the institutional review board of Nara Medical University, and the study was performed in accordance with the Declaration of Helsinki.

2.2 | Measures

Caregiver burden was measured by using the 22-item Zarit Caregiver Burden Interview (ZBI) whose item is scored from 0 to 4 (0-88 points).[16] There is no definite cut off point. Burden because of the 3 factors of psychosocial, dependency, and guilt was calculated as the mean of the 3 separate factors.[17] The psychosocial burden factor represents caregiver burden of primarily affective. The dependency burden factor is associated with strained tangible resources, such as utilization of time and money. The guilt factor is associated with how well the caregiver thinks he or she is meeting the standards of an "ideal" caregiver. Psychosocial burden subscales included the following: 4, feels embarrassed; 5, feels angry; 6, relative affects relationships with others in negative way; 9, feels strained; 11, does not have privacy; 12, social life has suffered; 13, feels uncomfortable about having friends over; 16, unable to take care of relative much longer; 18, wishes to leave the care to someone else; 19, feels uncertain; and 22, feels burdened. Dependency burden subscales included the following: 1, relative asks for more help than he/she needs; 2, not enough time for oneself due to time with relative; 3, stressed from trying to balance care and family/work responsibilities; 8, relative is dependent; 10, health has suffered because of involvement with relative; 14, are the only one that relative depends on; and 15, not enough money to take care of relative. Guilt burden included the following: 7, afraid of what the future holds for your relative; 20, should be doing more for your relative; and 21, could do a better job in caring for relative. Patients' frontal lobe functions were assessed by using the FAB tool,[11] which includes 6 subtests: (1) conceptualization, (2) mental flexibility, (3) motor programming, (4) sensitivity to interference, (5) inhibitory control, and (6) environmental autonomy. The total score is 18, and higher scores indicate better frontal functioning. Patients' cognitive dysfunction was evaluated by using the MMSE.[18] Mini-Mental State Examination contains 11 items (0-30 points) and has a cut-off score of 27 for detecting cognitive dysfunction. Neuropsychiatric symptoms were assessed by using the Neuropsychiatric Inventory Questionnaire (NPI).[19] The NPI consisted of 12 items, which allows for a total score of 0 to 36 points. The NPI does not have a definite cut off score. Depression was assessed by using the 15-item Geriatric Depression Scale (0-15 points).[20] Geriatric Depression Scale is a self-report measure of depression in older adults. Seven points were often considered as the cut point, although there are various opinions. Functional capabilities were assessed by using the Physical Self-Maintenance Scale (PSMS).[21] The PSMS consists of 6 items regarding toileting, feeding, dressing, grooming, physical ambulation, and bathing. Each item is scored from 0 (no impairment) to 4 (severe impairment), which allows for a total score of 0 to 24 points.

2.3 | Magnetic resonance imaging data acquisition

All MRI examinations were performed by using a 3.0-T clinical scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 32-channel phased-array brain coil. High-resolution 3-dimensional T1-weighted images were acquired by using a magnetization-prepared rapid gradient-echo sequence (TR: 1800 ms, TE: 2.4 ms, flip angle: 10°, FOV: 256 mm, 208 sections in the sagittal plane, acquisition matrix: 256 × 256, and acquired resolution: 1 × 1 × 1 mm).

2.4 | Image processing

Image preprocessing was performed by using SPM12 software (Wellcome Department of Imaging, Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), Matlab R2014a (MathWorks, Natick, MA, USA), and the Computational Anatomy Toolbox for SPM (CAT12; http://dbm.neuro.uni-jena.de/cat/). We applied the default preprocessing approach in CAT12. The T1-weighted images underwent bias correction; tissue segmentation into gray matter (GM), white matter, and cerebrospinal fluid; and registration using linear transformations (affine registration) and nonlinear transformations using diffeomorphic anatomical registration through exponentiated lie algebra[22] within a unified model. The analyses were subsequently focused on the GM segments, which were multiplied by the nonlinear components that were derived from the normalization matrix, to preserve the actual local GM values (modulated GM volumes). The modulated and normalized GM segments (voxel size: 1.5 × 1.5 × 1.5 mm) were ultimately smoothed by using a Gaussian kernel of 8 mm full-width at half-maximum.

2.5 | Voxel-based analysis

Exploratory voxel-based analysis was performed by using SPM12 software to examine the correlations between the GM values and the FAB total scores for the patients with AD. Global scaling using the total intracranial volume was used to correct for different brain sizes. To avoid possible edge effects between the different tissue types, we excluded all voxels outside of the GM by using absolute threshold masking. The mean total intracranial volume was 1434 cm^3, and all images were globally scaled to a value of 50, which corresponded to overall scaling of 50/1434. To obtain an absolute threshold of 0.2, we used 0.2 × 50/1434, and we applied a liberal threshold of $P < .001$ with an extent of 300 voxels across the whole brain. Spherical volumes of interest (VOIs, radius: 3 mm) were placed in the regions where significant correlations were observed, and the regional volumes were calculated by averaging the values for all voxels within the VOIs.

2.6 | Statistical analyses

Statistical analysis was performed by using IBM SPSS software (version 21.0J; IBM Corp., Armonk, NY, USA). Spearman's correlation coefficient was used to evaluate the correlation between psychometric scores, as well as the correlations between the GM volumes in the VOIs, caregiver ZBI scores and dependency burden factor, and FAB total scores. These analyses were performed to confirm the SPM12 results. A *P*-value of <.05 was considered statistically significant.

Path analysis was used to estimate the relationships between the regional GM volumes in the VOIs, the FAB total scores, and the caregiver ZBI scores. The model's fit was evaluated by using the χ^2 test, normed fit index (NFI), and comparative fit index (CFI). The χ^2 value describes the discrepancy between the study sample and the fitted covariance matrices, with *P*-values of >.05 indicating a good model fit. The NFI assesses the discrepancy between the χ^2 values of the existing and null models, and the fit is considered good at values of >.9.[23] The CFI is a revised form that evaluates the discrepancy between the exiting and hypothesized models, and the fit is considered good at values of ≥.95.[24]

3 | RESULTS

3.1 | Demographic and clinical data

The patients' characteristics are presented in Table 1. Consistent with the findings of our previous study,[10] the FAB total scores were correlated with the total ZBI scores ($r = -.40$, $P = .045$) and the dependency burden factor from the ZBI ($r = -.46$, $P = .018$). There were not significant FAB correlations with NPI ($r = -.30$, $P = .135$) nor PSMS ($r = -.16$, $P = .437$).

TABLE 1 Patient characteristics

	Mean ± SD or Frequency (%)	Range
Age (years)	73.0 ± 9.9	46-89
Sex		
Male	7 (26.9%)	-
Female	19 (73.1%)	-
Education (years)	11.5 ± 2.2	8-16
Measurements		
ZBI		
The total scores	12.2 ± 10.9	1-38
The psychosocial burden factor	0.4 ± 0.5	0-1.6
The dependency burden factor	0.7 ± 0.6	0-2.1
The guilt factor	0.9 ± 0.8	0-3.0
FAB	14.2 ± 3.5	4-18
MMSE	22.6 ± 3.2	13-26
NPI	2.8 ± 4.1	0-16
PSMS	0.9 ± 1.7	0-7
GDS	3.7 ± 3.6	0-12

Abbreviations: SD, standard deviation; ZBI, Zarit Burden Interview; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; GDS, Geriatric Depression Scale.

3.2 | Correlation of Frontal Assessment Battery total scores with regional gray matter volumes

The voxel-based analysis revealed a significant positive correlation of the FAB total scores with the volume of the left dorsolateral prefrontal cortex (DLPFC; (*x*, *y*, *z*) = (−23, 29, 51), Brodmann area: 8, and cluster voxel size: 393, T: 6.00) (Figure 1). There was no significant negative correlation of the FAB total scores with the regional GM volumes. The VOI analysis confirmed a significant positive correlation between the FAB total scores and the volume of the left DLPFC in patients with AD (r = .71, P < .001) (Figure 2). Although we found a significant positive correlation of the FAB total scores with the MMSE scores (r = .44, P = .024), the positive correlation of the FAB total scores with the volume of the left DLPFC remained significant (r = .70, P < .001) after controlling for the effect of general cognitive dysfunction based on the MMSE (Table 2). When we examined the relationship between the left DLPFC volume and the ZBI total and subscores, there were significant correlations between the volume of the left DLPFC and total ZBI scores and the dependency burden factor (Table 3).

3.3 | Path analysis results

Path analysis was used to estimate the relationships between the volume of the left DLPFC, FAB total scores, and caregiver burden (dependency burden factor from the ZBI) (Figure 3). The hypothesized model was valid and fit the data well under the null hypothesis that the model fit the data (χ^2 (1) = 2.45, P = .12). Furthermore, the fit indices for our model satisfied the criteria for a good fit (CFI = .96; NFI = .94).

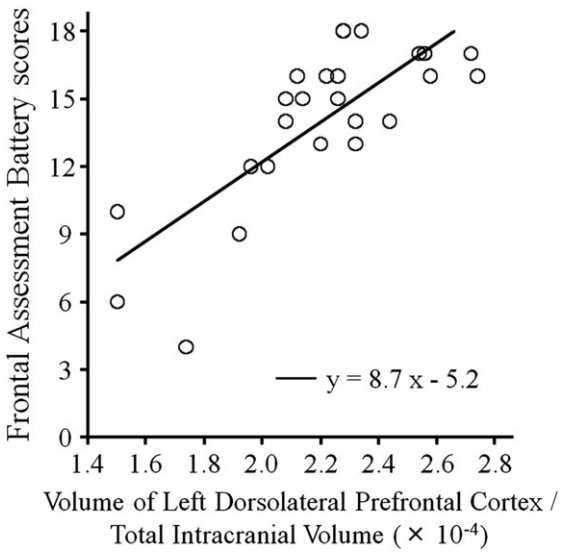

FIGURE 2 Scatterplots showing a significant positive correlation between Frontal Assessment Battery scores and the left dorsolateral prefrontal cortex volumes. Spherical volumes of interest were placed on the region that had a significant positive correlation with the Frontal Assessment Battery scores in the voxel-based analysis. This revealed a significant positive correlation with the Frontal Assessment Battery scores (r = .71, P < .001).

4 | DISCUSSION

The present study revealed that FAB total scores were correlated with regional volumes that were centered on Brodmann area 8 (the left DLPFC). In this context, the DLPFC is thought to play important roles in frontal lobe functions, such as attention, planning, sequencing, and

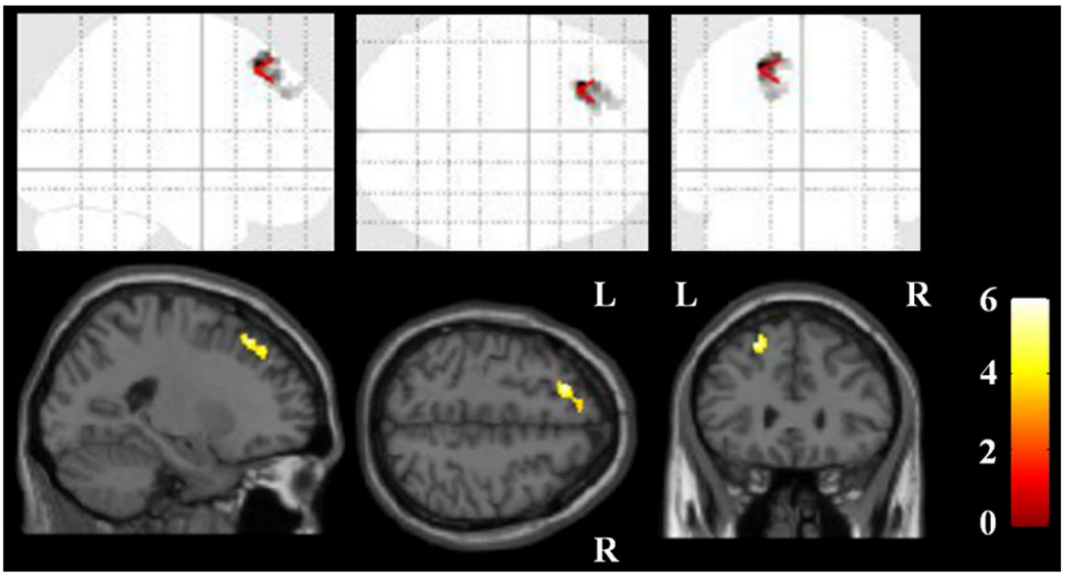

FIGURE 1 Gray matter regions that were positively correlated with Frontal Assessment Battery (FAB) scores. Gray matter (GM) volume was positively correlated with Frontal Assessment Battery (FAB) scores in the voxel-based analysis. The detected areas have an uncorrected P-value of .001 in ≥300 contiguous voxels. These parametric mapping projections were then superimposed on representative transaxial (z = 51), sagittal (x = −23), and coronal (y = 29) magnetic resonance images. There was no significant negative correlation between the FAB scores and regional GM volumes [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Correlations of the volume of the left dorsolateral prefrontal cortex/the total intracranial volume with the total Frontal Assessment Battery score

	r	*P*
Spearman's rank correlation coefficient	0.71	<.001
Partial correlation coefficient from the MMSE	0.70	<.001

Abbreviations: FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination.

working memory.[25] Some imaging studies have also revealed that frontal lobe functions were associated with the DLPFC, based on assessments using the regional metabolism of fluorodeoxyglucose during positron emission imaging[26] or regional blood perfusion during single-photon emission computed tomography imaging.[27] Thus, regional atrophy and dysfunction of the DLPFC may contribute to reduced control of attention and sensitivity to interference, based on the FAB scores from the present study.

Although the FAB was design to assess different aspects of frontal lobe functioning,[11] there is controversy regarding whether FAB scores actually reflect frontal lobe functions. For example, some evidence suggests that FAB scores are associated with general cognitive decline, but not specifically with frontal lobe functions.[13,14] Furthermore, the present study also revealed a positive correlation between the FAB total scores and the MMSE scores. However, after controlling for the effect of the MMSE scores, we found that the FAB total scores were still correlated with the volume of the left DLPFC. Thus, it appears that the FAB is an appropriate tool for assessing frontal lobe functions.

There is accumulating evidence regarding the effects of dementia on the caregiver's physical and mental status.[2-8] Those results highlight the need for interventions that can reduce caregiver burden. For example, financial support provided to patients with dementia and their caregivers was associated with decreased care time.[28] Furthermore, cognitive functions and neuropsychological symptoms can help predict caregiver burden.[29-31] Moreover, we observed that FAB total scores were associated with caregiver burden, and especially the dependency factor. Frontal lobe dysfunction assessed by FAB can be a good predictor of the caregiver's burden regardless of the identification of a biomarker. Further, few studies have examined the relationship between caregiver burden and brain structural changes. The present study provides objective evidence that frontal dysfunction, caused by atrophy of the left DLPFC, resulted in greater caregiver burden, which may facilitate the development of a biomarker for predicting caregiver burden.

FIGURE 3 A path analysis model of the relationships between the Frontal Assessment Battery total scores, the dependency burden factor from the Zarit Burden Interview, and the spherical volumes of interest in the left dorsolateral prefrontal cortex/the total intracranial volume. The standardized regression weights are shown for the path analysis model of the relationships between the spherical volumes of interest in the left dorsolateral prefrontal cortex (DLPFC)/the total intracranial volume (TIV), the Frontal Assessment Battery (FAB) total scores, and the dependency burden factor from the Zarit Burden Interview (ZBI). $^{**}P < .001$.

The present study has several limitations that deserve consideration. First, the small sample size is associated with known risks of bias, and further, large-scale studies are needed to validate our findings. Second, the reliability of FAB should be examined using another psychometric test that is specific for frontal lobe function, such as the Wisconsin Card Sorting Test. Additional studies are needed to determine the reliability to the present results and to provide a more detailed understanding of the significance of the FAB scores.

TABLE 3 The associations between the volume of the left dorsolateral prefrontal cortex/the total intracranial volume, the Frontal Assessment Battery, and Zarit Burden Interview scores

Variables	Mean ± SD	Range	*r* (*P*)[a]
The associations of volume of the left dorsolateral prefrontal cortex/the total intracranial volume			
FAB	14.2 ± 3.5	4-18	0.71 (<.001)
ZBI	12.2 ± 10.9	1-38	−0.60 (.001)
The dependency burden factor of the ZBI	0.7 ± 0.6	0-2.1	−0.51 (.007)
The associations of the FAB			
The psychosocial burden factor of the ZBI	0.4 ± 0.5	0-1.6	−0.28 (.161)
The dependency burden factor of the ZBI	0.7 ± 0.6	0-2.1	−0.46 (.018)
The guilt factor of the ZBI	0.9 ± 0.8	0-3.0	−0.25 (.220)

Abbreviations: SD, standard deviation; ZBI, Zarit Burden Interview; FAB, Frontal Assessment Battery.

[a]Spearman's rank correlation coefficient analysis to evaluate the correlations with the volume of the left dorsolateral prefrontal cortex/the total intracranial volume and the Frontal Assessment Battery.

5 | CONCLUSION

The present study revealed that decreased FAB total scores were significantly associated with a smaller volume of the left DLPFC in patients with AD, which contributed to greater caregiver burden, especially regarding the dependency factor. Furthermore, the results indicate that the FAB was a reliable tool for evaluating frontal lobe functions while accounting for general cognitive dysfunction. Moreover, we created a model of the associations between the volume of the left DLPFC, FAB total scores, and caregiver burden, especially the dependency factor. This model may facilitate the development of an objective biomarker for predicting caregiver burden, which could help reduce the physical and mental deterioration of caregivers for patients with AD.

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CONFLICT OF INTEREST

The authors have no disclosures to report.

AUTHOR CONTRIBUTIONS

KM and FY designed the study and collected, analyzed, and interpreted the data. JI and TK designed the study and interpreted the data. TM and KK collected and analyzed the MRI data. AH, MT, and KK analyzed and interpreted the data. KM wrote the manuscript. All authors reviewed and edited the manuscript.

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